PATENT COOPERATION TREATY

HM | AHF | Julie

From the
INTERNATIONAL SEARCHING AUTHORITY

To: DOCKETED

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Docket No: PR60507WO
Attorney: AHF
Paper: Written Opinion
Due Date: 19 JUL 05
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PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY
(PCT Rule 43*bis*.1)

Date of mailing (day/month/year) 19/05/2005 see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220 PR 60507 WO

FOR FURTHER ACTION
See paragraph 2 below

International application No.	International filing date (day/month/year)	Priority date (day/month/year)
PCT/US2004/032918	04.10.2004	08.10.2003

International Patent Classification (IPC) or both national classification and IPC
C07D333/38, C07D307/54, C07D261/18, C07D211/14, A61K31/495, A61K31/381, A61K31/341, A61P15/02,

Applicant
SMITHKLINE BEECHAM CORPORATION

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☒ Box No. VII Certain defects in the international application
- ☒ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

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Name and mailing address of the ISA:

European Patent Office
D-80298 Munich
Tel. +49 89 2399 - 0 Tx: 523656 epmu d
Fax: +49 89 2399 - 4465

Authorized Officer

Stroeter, T

Telephone No. +49 89 2399-8088

Form (PCT/ISA/237) (Cover Sheet) (January 2004)
Express Mail Label No.
EV 332064734 US

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/US2004/032918

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

   ☐ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☐ in written format

   ☐ in computer readable form

   c. time of filing/furnishing:

   ☐ contained in the international application as filed.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 6-11(in part) and 22-24

because:

☒ the said international application, or the said claims Nos. 22-24 relate to the following subject matter which does not require an international preliminary examination *(specify)*:

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for the whole application or for said claims Nos. 6-11 (in part)

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form	☐	has not been furnished
	☐	does not comply with the standard
the computer readable form	☐	has not been furnished
	☐	does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-36
	No:	Claims	
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-36
Industrial applicability (IA)	Yes:	Claims	1-21, 25-36
	No:	Claims	

2. Citations and explanations

see separate sheet

Box No. VII Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

see separate sheet

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

Express Mail Label No.
EV 332064734 US

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY (SEPARATE SHEET)

International application No.
PCT/US2004/032918

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

(1) Present claims 6-11 relate to compounds defined by reference to a desirable characteristic or property, namely a certain "improvement in bioavailability in a rat". The claims cover all compounds having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for only a very limited number of such compounds. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope was impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the compounds by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible.

Consequently, the search for claims 6-11 had been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to the compounds of formula (I) as defined in claim 1 and thus the examination will likewise only be carried out such subject-matter, i.e. compounds wherein $R^* = R^1$.

2 Prior art documents

(2) Claims 22-24 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1 Subject-matter of the independent claims

The present application is directed to triphenylethylene type compounds, i.e. certain 1,1,2-triphenylbuten compounds, which are active as SERM (selective estrogen receptor modulator) prodrugs providing an increased bioavailability through an acyloxy substituent (instead of an OH group) attached to one of the phenyl rings. These compounds are said to be useful in the treatment of various diseases such as menopausal disorders, osteoporosis, female sexual dysfunction, breast cancer etc.

The claims are drawn to said products (independent claims 1 and 6), pharmaceutical compositions (independent claim 14) comprising such compounds, the use of these compounds for the manufacture of medicaments (independent claims 19 and 20), methods of treatment/prophylaxis (independent claims 22 and 23), a process for making these compounds (independent claim 25) and certain intermediates (independent claim 33).

2 Prior art documents

Reference is made to the following documents. The given numbering will be adhered to in the rest of the procedure:

D1: WO 01/77057 A 18 October 2001
D2: SCANLAN T S ET AL, CHEMISTRY AND BIOLOGY, CURRENT BIOLOGY, LONDON, GB, vol. 8, no. 5, 2001, pages 427-436
D3: WO 01/77055 A 18 October 2001
D4: WO 03/016270 A 27 February 2003
D5: WO 92/04310 A 19 March 1992
D6: WILLSON T M ET AL, vol. 37, no. 11, 25 May 1994, pages 1550-1552

3 Novelty (Article 33(2) PCT)

The presently claimed compounds of formula (I) as defined in claim 1 and the intermediates of formula (IV) differ from the structurally most related compounds in D1-D6 through the side group R^1-O being the main distinguishing structural feature. Thus, compound claims 1-13 and consequently further claims 14-32 as well as claims 33-36 appear to be novel.

4 Inventive step (Article 33(3) PCT)

SERM modulators of the triphenylethylene type in which one of the phenyl ring is substituted in para-position with a heteroatom (focus on present group R^1-O) are known from D1 and D2:
D1 reveals compounds having a halogen atom instead of an oxy substituent
D2 reveals compound 16 having an OH group

The present problem to be solved is the provision of prodrug forms of the known compound 16 (Z isomer) of D2 which have an increased bioavailability compared to the D2 compound.

This problem was solved by modifying the prior art compound, i.e. replacing the H of the OH group with an acyl group R^1. This solution, however, appears to be obvious in the light of documents D3 or D4 which refer to suitable prodrug forms (acid derivatives) of alcohol functional groups of related compounds (see page 18, line 12-34 of D3 and page 22, line 23 - page 23, line 7 of D4). The skilled man could therefore expect an enhanced bioavailability when replacing the H in OH with acyl groups. Such prodrug forms are known to increase the lipophilicity (as in the compounds of D1 which lack the OH group) and to provide a cleavable bonding between the O atom and the modifying group.

Therefore it appears that the subject-matter of claims 1-13 and consequently further claims 14-32 as well as claims 33-36 lacks an inventive step.

5 Industrial applicability (Article 33(4) PCT)

The subject-matter of the present claims 1-21 and 25-36 is in accordance with the requirements of Article 33(4) PCT.

For the assessment of the present claims 22-24 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Re Item VII
Certain defects in the international application

(1) The requirements of Rule 5.1(a)(ii) PCT are not met since the relevant background art (documents D1 and D2) have not been identified in the description, i.a. no reference for compound 1 which is not part of the claims is given.

(2) Claims 4 and 5 should have been formulated as dependent claims (on e.g. claim 1).

Re Item VIII
Certain observations on the international application

Formulae (IV) and (V) are not correct because the C=O group attached to both O and R^1 appears to be superfluous (claims 25 and 33.